SCIENCE CHINA
Life Sciences

Special Topic: Organ/Tissue-specific immunity
• EDITORIAL •

December 2016 Vol.59 No.12: 1205–1209
doi: 10.1007/s11427-016-0351-y

Regional immunity in tissue homeostasis and diseases

Zhigang Tian[1*], Xuetao Cao[2**], Yongyan Chen[1] & Qunyan Lyu[3]

[1]*Institute of Immunology and The CAS Key Laboratory of Innate Immunity and Chronic Disease, School of Life Sciences and Medical Center, University of Science & Technology of China, Hefei 230027, China;*
[2]*National Key Laboratory of Medical Immunology & Institute of Immunology, Second Military Medical University, Shanghai 200433, China;*
[3]*Department of Health Sciences, National Natural Science Foundation of China, Beijing 100085, China*

Received November 17, 2016; accepted November 22, 2016; published online December 3, 2016

Citation: Tian, Z., Chen, X., Chen, Y., and Lyu, Q. (2016). Regional immunity in tissue homeostasis and diseases. Sci China Life Sci 59, 1205–1209. doi: 10.1007/s11427-016-0351-y

The immune system functions in the organ/tissue of the body. The immune cell differentiation and function are influenced by the organ/tissue microenvironments in which they reside, and the interaction of immune cells with the organ/tissue microenvironments may affect and even determine the outcome of the immune responses (Hu and Pasare, 2013; Zajac and Harrington, 2014). It has been increasingly appreciated that the immunologic characterization from professional immune organs including thymus, bone marrow, spleen, and lymph node, is greatly distinguished from that in mucosal immune organs including skin, intestine, lung, pancreas, uterus and kidney, and other organs such as liver, bone, brain, maternal-fetal interface, and so on. Each organ/tissue is characterized with its own anatomy and microenvironment, in which immune cell populations and subsets may have unique functional molecules, forming "unique regional immune features". The regional immune responses play an important role in tissue homeostasis and are extensively involved in the pathogenesis of the major diseases related to each tissue/organ.

With the research progressed, a more clear description of the regional immune features has been presented, such as novel tissue-resident immune cell subsets, organ-specialized immune recognition, organ-specific factors instructing regional immune responses in liver, lung, intestine, bone, brain, uterus, adipose, kidney, tumor, etc. For example, specialized tissue-resident macrophages, including Kupffer cells in the liver, alveolar macrophages in the lung, microglia in the brain, osteoclasts in the bone, and histiocytes in the intestinal connective tissue, exhibit distinct functions due to their resident tissue (Murray and Wynn, 2011). Specialized tissue-resident regulatory T cells in the visceral adipose tissue (VAT Tregs), muscle Tregs, bone Tregs and skin memory Tregs, have also been reported with their unique functions in local tissues (Zhou et al., 2015). Innate immune cells continuously receive signals from the resident environment, such as commensal microbiota signals in mucosal organs, which will influence the outcome of immune responses. In this issue, Zhang et al. reviewed the innate recognition of microbial-derived signals in immunity and inflammation (Zhang and Liang, 2016), which will help us understand the local immune responses.

Liver is an unique organ with predominant innate immunity, enriched with Kupffer cells, NK cells, NKT cells and γδ T cells (Gao et al., 2008). Current studies have revealed that NK cells are not a homogeneous population, but instead consist of distinct subsets including conventional NK (cNK) cells and tissue-resident NK (trNK) cells. In this issue, Peng

*Corresponding author (email: tzg@ustc.edu.cn)
**Corresponding author (email: caoxt@immunol.org)

and Tian summarized the phenotypic and functional features of liver trNK cells (Peng and Tian, 2016). In mice, liver NK cells can be divided into two distinct subsets: $CD49a^{-}DX5^{+}$ cNK and $CD49a^{+}DX5^{-}$ trNK cells which reside in the liver sinusoid blood and confer memory-like responses in contact hypersensitivity (CHS) models (Peng et al., 2013). Liver trNK cells and cNK cells require different transcription factors for their development, thus representing separate developmental lineages (Constantinides et al., 2014; Daussy et al., 2014; Klose et al., 2014; Mackay et al., 2016). They also overviewed recent advances in human liver trNK cells and discussed the striking shared hallmarks of trNK cells in different tissues. Human hepatic $CD56^{bright}$ NK cells express trNK cell markers such as CD69 and CXCR6, and exhibit unique transcriptiona profiles compared to cNK cells (Hudspeth et al., 2016). Similar to murine liver trNK cells, a proportion of human hepatic $CD56^{bright}$ NK cells with the expression of CD49a are $T\text{-}bet^{+}Eomes^{-}$ (Marquardt et al., 2015). Additionally, in this issue Han et al. identified a new subset of inflammation-induced $CD69^{+}$ Kupffer cells during *Listeria monocytogenes* infection (Zhang et al., 2016). Hepatic $CD69^{+}$ Kupffer cells expressed higher levels of CD11b, but produced lower levels of F4/80, which could not be depleted by clodronate liposome administration. Hepatic $CD69^{+}$ Kupffer cells suppressed Ag-nonspecific and OVA-specific $CD4^{+}$ T cell proliferation through membrane-bound TGF-β1 (mTGF-β1). $CD69^{+}$ Kupffer cells may contribute to protect host from pathological injure by preventing immune over-activation.

During human pregnancy, an orchestrated evolutionary maternal adaption toward tolerance of the semiallogeneic fetus is required. In the decidua, remodeling of the immune system involves NK cells, macrophages, T cells and DCs to alter the local microenvironment (Fu et al., 2014; Lima et al., 2014). NK cells as the largest population of immune cells during the first trimester in human decidua, accounting for 50%–70% of the total number of immune cells after 9–12 weeks of pregnancy, showed a close reaction to invasive fetal trophoblasts and stromal cells (Colucci and Kieckbusch, 2015; Tao et al., 2015). Evidence shows decidual NK cells act as sentinel cells to control local inflammation and tolerance, and mediate the regulation of fetal growth. In this issue, Fu et al. summarized the concepts and rationale for the remodeled immune system during pregnancy, and the formation and education of decidual NK cells (Fu and Wei, 2016). Most decidual NK cells are $CD56^{bright}CD16^{-}$ NK cells, which express CXCR4, and can be selectively recruited into the decidua by interaction with chemokine CXCL12 secreted by DSCs and EVTs (Hanna et al., 2003; Wu et al., 2005).

Adipose tissues, including white, brown and beige fat, play pivotal roles in metabolic homeostasis (Rosen and Spiegelman, 2014). Macrophages, mast cells, neutrophils, eosinophils, ILC2, T cells and B cells have all been found in adipose tissue and were involved in obesity-related metabolic dysfunctions (Cipolletta et al., 2012; Feuerer et al., 2009; Liu et al., 2009; Lynch et al., 2012; Molofsky et al., 2013; Talukdar et al., 2012; Winer et al., 2009; Winer et al., 2011; Wu et al., 2011). Particularly, macrophages as the critical effector cells in orchestrating inflammation have been most extensively investigated to explore their roles in obesity-associated metabolic inflammation and insulin resistance (McNelis and Olefsky, 2014). In this issue, Qiu et al. reviewed the metabolic activation and functional properties of adipose tissue macrophage (ATM) including M1 and M2 macrophages (Qiu et al., 2016), which would help us better understand the pathogenic and/or protective roles of ATM and the translational opportunities for developing novel therapeutics against obesity, type 2 diabetes and other related metabolic diseases.

Osteoimmunology was firstly introduced in 2000, indicating the bone and immune system have an intense interaction and should be considered as a functional unit (Arron and Choi, 2000). Osteoblasts (OBs) contribute to hematopoietic progenitor growth and HSC pool maintenance through Notch signal and osteopontin (OPN) production (Calvi et al., 2003; Nilsson et al., 2005). The development and response of immune cells associate to bone remodeling; on the other hand, activated immune cells are involved in bone metabolism regulation, and mediate osteoporosis and bone erosion under pathological conditions such as rheumatoid arthritis (RA), spondyloarthropathy (SPA), osteoporosis (OP), and periodontal disease (PD). In this issue, Zhao et al. presented current understanding of osteoimmunology and emphasized on the RANK/RANKL/OPG signaling in bone remodeling and immune responses (Zhao et al., 2016). Recent research progress in the interactions between T cells, B cells, DCs and bone cells, in the role of several kinds of cytokines including M-CSF, TNF-α, IL-1, IFN-γ, IL-4, IL-10, IL-6, TGF-β, OPN and complement system in bone homeostasis were also summarized in this review, particularly their pathogenesis in major diseases.

The central nervous system (CNS) as an immune privileged organ, owns its local tissue barrier and immunosuppressive microenvironment. Interestingly, Glial cells including activated microglia and astrocytes, participate in local immune regulation within the CNS. Further, a specialized CNS-cytokine network was constituted and regulated the development and recovery from autoimmune diseases within the CNS (Xiao and Link, 1998). Additionally, numerous myeloid cell subsets were found in CNS-adjoining tissues, namely the meninges, the perivascular space, and the choroid plexus (Brendecke and Prinz, 2015). These immune cells have been demonstrated to be involved in the initiation, progression and resolution of multiple sclerosis (MS). In this issue, Yan et al. reported a unique group of patients with neu-

romyelitis optica spectrum disorder (NMOSD) who carried autoantibodies of aquaporin-4 (AQP4) and myelin-oligodendrocyte glycoprotein (MOG) (Yan et al., 2016). They found NMOSD patients carrying both anti-AQP4 and anti-MOG antibodies exhibited combined features of prototypic NMO and relapsing-remitting form of MS, whereas NMOSD with only anti- MOG antibody exhibited an "intermediate" phenotype between NMOSD and MS, indicating that anti-MOG antibody might be pathogenic in NMOSD patients and that determination of anti-MOG antibody may be instructive for management of NMOSD patients.

The kidney has its unique organizational structure and physiological functions. It has been known recruitment of leukocytes into the kidney occurs in capillaries of the renal glomeruli and in postcapillary venules of the renal cortex, which is tissue-specific (Rossaint and Zarbock, 2013). Kidney diseases are protean, such as acute kidney injury (AKI), autoimmune glomerulonephritis, and rejection of kidney transplants. Strong evidence demonstrates immune cells, predominantly DCs and macrophages determine both renal tissue injury and subsequent reparative responses (Rogers et al., 2014). However, direct kidney injury mediated by renal infiltrated T cells has not been clearly elucidated in humans. In this issue, Hu et al. detected different types of T cells and macrophages in the renal biopsy tissues from patients of anti-glomerular basement membrane (GBM) disease (Hu et al., 2016). They found that the distribution of T cells was predominant in the peri-glomerular and interstitial areas, particularly, the infiltrating $CD8^+$ T cells correlated with the percentage of ruptured Bowman's capsules, which may participate in the pathogenic mechanism of glomerular damage.

Tumor tissue is also a kind of important regional immune response area. Tumor associated immune cells undergo phenotypic and functional alterations due to the tumor microenvironments (Liu and Cao, 2015a; Liu and Cao, 2015b). In this issue, Xie et al. reported lactic acid in tumor microenvironments inhibited the production of IFN-γ and IL-4 in NKT cells, and these dysfunctions of NKT cells could simply be induced by low extracellular pH through inhibiting mTOR signaling (Xie et al., 2016). It is interesting that tumor acidic microenvironments could regulate immune cell response through modulating cellular metabolisms. Additionally, in the tumor microenvironment a variety of immune factors will alter and aggravate the disease process. Also, Lu et al. reported IL-17 could inhibit the formation of malignant pleural effusion (MPE) via promoting the differentiation of Th9 and Th2 cells in the tumor microenvironments (Lu et al., 2016).

Based on the characteristics of regional immune responses, the future research will focus on discovering novel immune cell subsets and their origin and development in certain types of tissue/organs, exploring the key functional molecules of the tissue-resident immune cell subsets and their interactions with tissue/organ microenvironments, clarifying their immunological mechanisms in organ-related major diseases, explaining the local environmental factors involved in the tissue residency, which will provide a theoretical basis for the prevention and control of these major diseases and reveal the possible immune intervention targets and immune treatment.

Compliance and ethics *The author(s) declare that they have no conflict of interest.*

Arron, J.R., and Choi, Y. (2000). Bone versus immune system. Nature 408, 535–536.

Brendecke, S.M., and Prinz, M. (2015). Do not judge a cell by its cover—diversity of CNS resident, adjoining and infiltrating myeloid cells in inflammation. Semin Immunopathol 37, 591–605.

Calvi, L.M., Adams, G.B., Weibrecht, K.W., Weber, J.M., Olson, D.P., Knight, M.C., Martin, R.P., Schipani, E., Divieti, P., Bringhurst, F.R., Milner, L.A., Kronenberg, H.M., and Scadden, D.T. (2003). Osteoblastic cells regulate the haematopoietic stem cell niche. Nature 425, 841–846.

Cipolletta, D., Feuerer, M., Li, A., Kamei, N., Lee, J., Shoelson, S.E., Benoist, C., and Mathis, D. (2012). PPAR-γ is a major driver of the accumulation and phenotype of adipose tissue Treg cells. Nature 486, 549–553.

Colucci, F., and Kieckbusch, J. (2015). Maternal uterine natural killer cells nurture fetal growth: in medio stat virtus. Trends Mol Med 21, 60–67.

Constantinides, M.G., McDonald, B.D., Verhoef, P.A., and Bendelac, A. (2014). A committed precursor to innate lymphoid cells. Nature 508, 397–401.

Daussy, C., Faure, F., Mayol, K., Viel, S., Gasteiger, G., Charrier, E., Bienvenu, J., Henry, T., Debien, E., Hasan, U.A., Marvel, J., Yoh, K., Takahashi, S., Prinz, I., de Bernard, S., Buffat, L., and Walzer, T. (2014). T-bet and Eomes instruct the development of two distinct natural killer cell lineages in the liver and in the bone marrow. J Exp Med 211, 563–577.

Feuerer, M., Herrero, L., Cipolletta, D., Naaz, A., Wong, J., Nayer, A., Lee, J., Goldfine, A.B., Benoist, C., Shoelson, S., and Mathis, D. (2009). Lean, but not obese, fat is enriched for a unique population of regulatory T cells that affect metabolic parameters. Nat Med 15, 930–939.

Fu, B., and Wei, H. (2016). Decidual natural killer cells and the immune microenvironment at the maternal-fetal interface. Sci China Life Sci 59, 1224–1231.

Fu, B., Tian, Z., and Wei, H. (2014). TH17 cells in human recurrent pregnancy loss and pre-eclampsia. Cell Mol Immunol 11, 564–570.

Gao, B., Jeong, W.I., and Tian, Z. (2008). Liver: an organ with predominant innate immunity. Hepatology 47, 729–736.

Hanna, J., Wald, O., Goldman-Wohl, D., Prus, D., Markel, G., Gazit, R., Katz, G., Haimov-Kochman, R., Fujii, N., Yagel, S., Peled, A., and Mandelboim, O. (2003). CXCL12 expression by invasive trophoblasts induces the specific migration of $CD16^-$ human natural killer cells. Blood 102, 1569–1577.

Hu, W., and Pasare, C. (2013). Location, location, location: tissue-specific regulation of immune responses. J Leukocyte Biol 94, 409–421.

Hudspeth, K., Donadon, M., Cimino, M., Pontarini, E., Tentorio, P., Preti, M., Hong, M., Bertoletti, A., Bicciato, S., Invernizzi, P., Lugli, E., Torzilli, G., Gershwin, M.E., and Mavilio, D. (2016). Human liver-resident $CD56^{bright}/CD16^{neg}$ NK cells are retained within hepatic sinusoids via the engagement of CCR5 and CXCR6 pathways. J Autoimmun 66, 40–50.

Hu, S., Jia, X., Li, J., Zheng, X., Ao, J., Liu, G., Cui, Z., and Zhao, M. (2016). T cell infiltration is associated with kidney injury in patients with anti-glomerular basement membrane disease. Sci China Life Sci 59, 1282–1289.

Klose, C.S.N., Flach, M., Möhle, L., Rogell, L., Hoyler, T., Ebert, K., Fabiunke, C., Pfeifer, D., Sexl, V., Fonseca-Pereira, D., Domingues, R.G., Veiga-Fernandes, H., Arnold, S.J., Busslinger, M., Dunay, I.R., Tanriver,

Y., and Diefenbach, A. (2014). Differentiation of type 1 ILCs from a common progenitor to all helper-like innate lymphoid cell lineages. Cell 157, 340–356.
Lima, P.D., Zhang, J., Dunk, C., Lye, S.J., and Anne Croy, B. (2014). Leukocyte driven-decidual angiogenesis in early pregnancy. Cell Mol Immunol 11, 522–537.
Liu, J., Divoux, A., Sun, J., Zhang, J., Clément, K., Glickman, J.N., Sukhova, G.K., Wolters, P.J., Du, J., Gorgun, C.Z., Doria, A., Libby, P., Blumberg, R.S., Kahn, B.B., Hotamisligil, G.S., and Shi, G.P. (2009). Genetic deficiency and pharmacological stabilization of mast cells reduce diet-induced obesity and diabetes in mice. Nat Med 15, 940–945.
Liu, Y., and Cao, X. (2015a). Intratumoral dendritic cells in the anti-tumor immune response. Cell Mol Immunol 12, 387–390.
Liu, Y., and Cao, X. (2015b). The origin and function of tumor-associated macrophages. Cell Mol Immunol 12, 1–4.
Lu, Y., Lin, H., Zhai, K., Wang, X., Zhou, Q., and Shi, H. (2016). Interleukin-17 inhibits development of malignant pleural effusion via interleukin-9-dependent mechanism. Sci China Life Sci 59, 1297–1304.
Lynch, L., Nowak, M., Varghese, B., Clark, J., Hogan, A.E., Toxavidis, V., Balk, S.P., O'Shea, D., O'Farrelly, C., and Exley, M.A. (2012). Adipose tissue invariant NKT cells protect against diet-induced obesity and metabolic disorder through regulatory cytokine production. Immunity 37, 574–587.
Mackay, L.K., Minnich, M., Kragten, N.A.M., Liao, Y., Nota, B., Seillet, C., Zaid, A., Man, K., Preston, S., Freestone, D., Braun, A., Wynne-Jones, E., Behr, F.M., Stark, R., Pellicci, D.G., Godfrey, D.I., Belz, G.T., Pellegrini, M., Gebhardt, T., Busslinger, M., Shi, W., Carbone, F.R., van Lier, R.A.W., Kallies, A., and van Gisbergen, K.P.J.M. (2016). Hobit and Blimp1 instruct a universal transcriptional program of tissue residency in lymphocytes. Science 352, 459–463.
Marquardt, N., Béziat, V., Nyström, S., Hengst, J., Ivarsson, M.A., Kekäläinen, E., Johansson, H., Mjösberg, J., Westgren, M., Lankisch, T.O., Wedemeyer, H., Ellis, E.C., Ljunggren, H.G., Michaëlsson, J., and Björkström, N.K. (2015). Cutting edge: identification and characterization of human intrahepatic CD49a$^+$ NK cells. J Immunol 194, 2467–2471.
McNelis, J.C., and Olefsky, J.M. (2014). Macrophages, immunity, and metabolic disease. Immunity 41, 36–48.
Molofsky, A.B., Nussbaum, J.C., Liang, H.E., Van Dyken, S.J., Cheng, L.E., Mohapatra, A., Chawla, A., and Locksley, R.M. (2013). Innate lymphoid type 2 cells sustain visceral adipose tissue eosinophils and alternatively activated macrophages. J Exp Med 210, 535–549.
Murray, P.J., and Wynn, T.A. (2011). Protective and pathogenic functions of macrophage subsets. Nat Rev Immunol 11, 723–737.
Nilsson, S.K., Johnston, H.M., Whitty, G.A., Williams, B., Webb, R.J., Denhardt, D.T., Bertoncello, I., Bendall, L.J., Simmons, P.J., and Haylock, D.N. (2005). Osteopontin, a key component of the hematopoietic stem cell niche and regulator of primitive hematopoietic progenitor cells. Blood 106, 1232–1239.
Peng H., and Tian Z. (2016). Tissue-resident natural killer cells in the livers. Sci China Life Sci 59, 1218–1223.
Peng, H., Jiang, X., Chen, Y., Sojka, D.K., Wei, H., Gao, X., Sun, R., Yokoyama, W.M., and Tian, Z. (2013). Liver-resident NK cells confer adaptive immunity in skin-contact inflammation. J Clin Invest 123, 1444–1456.
Qiu, Y., Shan, B., Yang, L., and Liu, Y. (2016). Adipose tissue macrophage in immune regulation of metabolism. Sci China Life Sci 59, 1232–1240.
Rogers, N.M., Ferenbach, D.A., Isenberg, J.S., Thomson, A.W., and Hughes, J. (2014). Dendritic cells and macrophages in the kidney: a spectrum of good and evil. Nat Rev Nephrol 10, 625–643.
Rosen, E.D., and Spiegelman, B.M. (2014). What we talk about when we talk about fat. Cell 156, 20–44.
Rossaint, J., and Zarbock, A. (2013). Tissue-specific neutrophil recruitment into the lung, liver, and kidney. J Innate Immun 5, 348–357.
Talukdar, S., Oh, D.Y., Bandyopadhyay, G., Li, D., Xu, J., McNelis, J., Lu, M., Li, P., Yan, Q., Zhu, Y., Ofrecio, J., Lin, M., Brenner, M.B., and Olefsky, J.M. (2012). Neutrophils mediate insulin resistance in mice fed a high-fat diet through secreted elastase. Nat Med 18, 1407–1412.
Tao, Y., Li, Y.H., Piao, H.L., Zhou, W.J., Zhang, D., Fu, Q., Wang, S.C., Li, D.J., and Du, M.R. (2015). CD56^{bright}CD25$^+$ NK cells are preferentially recruited to the maternal/fetal interface in early human pregnancy. Cell Mol Immunol 12, 77–86.
Winer, D.A., Winer, S., Shen, L., Wadia, P.P., Yantha, J., Paltser, G., Tsui, H., Wu, P., Davidson, M.G., Alonso, M.N., Leong, H.X., Glassford, A., Caimol, M., Kenkel, J.A., Tedder, T.F., McLaughlin, T., Miklos, D.B., Dosch, H.M., and Engleman, E.G. (2011). B cells promote insulin resistance through modulation of T cells and production of pathogenic IgG antibodies. Nat Med 17, 610–617.
Winer, S., Chan, Y., Paltser, G., Truong, D., Tsui, H., Bahrami, J., Dorfman, R., Wang, Y., Zielenski, J., Mastronardi, F., Maezawa, Y., Drucker, D.J., Engleman, E., Winer, D., and Dosch, H.M. (2009). Normalization of obesity-associated insulin resistance through immunotherapy. Nat Med 15, 921–929.
Wu, D., Molofsky, A.B., Liang, H.E., Ricardo-Gonzalez, R.R., Jouihan, H.A., Bando, J.K., Chawla, A., and Locksley, R.M. (2011). Eosinophils sustain adipose alternatively activated macrophages associated with glucose homeostasis. Science 332, 243–247.
Wu, X., Jin, L.P., Yuan, M.M., Zhu, Y., Wang, M.Y., and Li, D.J. (2005). Human first-trimester trophoblast cells recruit CD56^{bright}CD16$^-$ NK cells into decidua by way of expressing and secreting of CXCL12/stromal cell-derived factor 1. J Immunol 175, 61–68.
Xiao, B.G., and Link, H. (1998). Immune regulation within the central nervous system. J Neurol Sci 157, 1–12.
Xie, D., Zhu, S., and Bai, L. (2016). Lactic acid in tumor microenvironments causes dysfunction of NKT cells. Sci China Life Sci 59, 1290–1296.
Yan, Y., Li, Y., Fu, Y., Yang, L., Su, L., Shi, K., Li, M., Liu, Q., Borazanci, A., Liu, Y., He, Y., Bennett, J.L., Vollmer, T.L., and Shi, F.D. (2016). Autoantibody to MOG suggests two distinct clinical subtypes of NMOSD. Sci China Life Sci 59, 1270–1281.
Zajac, A.J., and Harrington, L.E. (2014). Tissue-resident T cells lose their S1P1 exit visas. Cell Mol Immunol 11, 221–223.
Zhang, X., Jiang, Z., Gu, Y., Liu, Y., Cao, X., and Han, Y. (2016). Inflammation-induced CD69$^+$ Kupffer cell feedback inhibits T cell proliferation via membrane-bound TGF-β1. Sci China Life Sci 59, 1259–1269.
Zhang, Y., and Liang C. (2016). Innate recognition of microbial-derived signals in immunity and inflammation. Sci China Life Sci 59, 1210–1217.
Zhao, L., Huang, L., and Zhang, X. (2016). Osteoimmunology: memorandum for rheumatologists. Sci China Life Sci 59, 1241–1258.
Zhou, X., Tang, J., Cao, H., Fan, H., and Li, B. (2015). Tissue resident regulatory T cells: novel therapeutic targets for human disease. Cell Mol Immunol 12, 543–552.

Biographical Sketch

Zhigang Tian is the current President of Chinese Society of Immunology (CSI) and Council member of International Union of Immunological Societies (IUIS) and Federation of Immunological Societies of Asia-Oceania (FIMSA), a professor at University of Science and Technology of China (USTC) in Hefei, China, where also works as a Director of Institute of Immunology, Director of The Key Lab of Innate Immunity and Chronic Diseases of Chinese Academy of Science, and President of Medical Center, and the former dean of School of Life Sciences of USTC. Zhigang used to work as a visiting scientist in NCI/NIH, USA during 1994–1996 and in Kanazawa University, Japan during 2002–2003. Currently, Tian's laboratory is credited with seminal discoveries regarding basic knowledge and clinical study of NK cells, particularly liver-resident NK cells, regulatory NK cell subsets, and NK cell-based immunotherapy. Zhigang is a co-Editor-in-Chief of *Cellular and Molecular Immunology*, and editorial board members of up to ten journals including *Hepatology*, *Journal of Autoimmunity*, *European Journal of Immunology* and *The Journal of Biological Chemistry*, and has published more than 250 papers in peer-reviewed journals including *Cell*, *Nature Immunology*, *Immunity*, *The Journal of Experimental Medicine*, *The Journal of Clinical Investigation*, *Nature Communications*, *Proceedings of the National Academy of Sciences of the United States of America*, etc.

Xuetao Cao is professor and President of Chinese Academy of Medical Sciences & Peking Union Medical College. He received Ph.D. from Second Military Medical University (Shanghai, China) in 1990, became Professor in Immunology in 1992 and Director of the Institute of Immunology in 2001 at the same University. He is Professor and Director of National Key Laboratory of Medical Immunology (2006.5–). He was elected as member of Chinese Academy of Engineering in 2005, Foreign Associate of German Academy of Sciences in 2013, and Foreign Member of EMBO in 2015. His major interests are innate response, inflammation and tumor immunotherapy. As corresponding author, he publishedmore than 230 original papers in peer-reviewed journals including *Cell*, *Nature*, *Science*. He is Co-Editor-in-Chief of *Cellular and Molecular Immunology*, editorial board member of *Cell*, *Annual Reviews of Immunology*, *Science Translational Medicine*, *eLife*, *Cell Research*, etc.

Yongyan Chen is an associate Professor of University of Science & Technology of China (USTC). As a member of Zhigang Tian's lab in USTC, she has been attempting to study the innate immunity of liver, including the biology of the overwhelming innate immune cells NK cells and NKT cells in the liver, and their roles during HBV infection and HBV-associated liver diseases; and the mechanisms of HBV-induced liver immunotolerance.

Qunyan Lyu, professor and Division Director, Division IV of Department of Health Sciences, National Natural Science Foundation of China. She received her Ph.D. in Mircobiology in 1993, and has been responsible for the management of natural science fund in the field of immunology or medical immunolgy for about 20 years. She has engaged herself in impletmenting the funding plans to support basic research, identifying and forstering scientifc talents, accepting project applications, organizing peer review process, administrating funded projects etc, in the field of immunology or medical immunolgy. As a professional scientific manager, she is also playing active roles in formulation of the priority funding areas, funding schemes, major research plans, annual funding arrangements as well as other disciplinary development strategies for the field of immunology or medical immunology.